ESSAYS ON APS CLASSIC PAPERS

The beginning of a fantastic, unanswered question: is 5-HT involved in systemic hypertension?

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This essay examines the historical significance of an APS classic paper that is freely available online:

Serotonin (5-hydroxytryptamine, 5-HT) was one of the first vasoactive amines to be discovered. As 5-HT is concentrated in the blood platelet to near millimolar concentrations, one might suspect that 5-HT would have significant impact as to how blood vessels, which carry the platelet, would function. In 1970, Don D. McGregor and Sir Horace Smirk (Figs. 1 and 2; kindly provided by Dr. Janet Ledingham, New Zealand) of the Otago University Medical School published a paper in the American Journal of Physiology (5) that began a line of research in hypertension investigating questions that are still being argued.

Their paper was entitled “Vascular response to 5-hydroxytryptamine in genetic and renal hypertensive rats” (5). The purpose of this study was to determine whether the mechanical advantage that an artery possessed in hypertension (thicker, stiffer wall compared with normal vessel) could completely explain the hyperreactivity to agonists, such that responses to agonists would be equivalently enhanced. Their experiments were straightforward and telling.

They used two models of hypertension. The first was an inbred strain of New Zealand rats that develop hypertension genetically (GH), and the second was a renal model of hypertension in which a small silver clip was placed on the renal artery of the right kidney (2 kidney, 1 clip). Normal Wistar rats were used as controls. The effects of intravenous 5-HT on arterial blood pressure was examined in the chloralose-anesthetized state. Additionally, mesenteric arterial perfusion pressure in the isolated mesenteric arcade exposed to 5-HT, norepinephrine (NE), or angiotensin II (ANG II) was also measured.

Rats with hypertension had a profound increase in reactivity to 5-HT. A dose of 5-HT that elevated blood pressure of Wistar rats by 47 mmHg increased arterial pressure of the GH rat by nearly twice as much (92 mmHg). When ganglionic transmission was blocked pharmacologically, blood pressure fell in both strains, but the GH continued to be more sensitive and reactive to 5-HT. This suggested that an element independent of the sympathetic nervous system/ganglionic activity was responsible for mediating the elevation in blood pressure; systemic arteries were a likely candidate. Their findings in the isolated perfused mesentery bear this idea out, as 5-HT was more potent and efficacious in the GH compared with Wistar. Similar enhancements to ANG II and NE were only modestly observed. These data provided the important evidence that it was not just the structural change the arteries from the hypertensive animal underwent (thicker media, stiffer wall) that caused hyperreactivity. At the time of this report, 5-HT receptors were not well defined and known only as “D” or “M” receptors (3). McGregor and Smirk (5) demonstrated that the increase in perfusion pressure to 5-HT could be blocked by a 5-HT receptor antagonist, xylamidine tosylate.

Thus began decades of research dedicated toward understanding how 5-HT may play a role in hypertension. A slew of studies using isolated arteries and arterial beds from different models of hypertension support the original finding of McGregor and Smirk (5). The threshold for arterial contraction/pressure increase to 5-HT was lower, potency of 5-HT higher, and the maximal effect 5-HT could cause also higher in the hypertensive rat compared with a normotensive control (for review, see Ref. 10). In 1979, Peroutka and Snyder (7) defined 5-HT1 and 5-HT2 receptors. Presently, 5-HT receptors are...
divided into seven different subtypes (5-HT₁ through 5-HT₇), and multiple subtypes of some of these receptors also exist. Development of selective serotonergic receptor agonists and antagonists allowed investigation as to which 5-HT receptor subtype was responsible for arterial contraction and whether this changed in hypertension. Investigators discovered that several 5-HT receptors (5-HT₁B/D, 5-HT₂A, 5-HT₂B, and 5-HT₇) are important in the vasculature. 5-HT could cause both contraction and relaxation in vascular beds. Introduction of ketanserin (Janssen Pharmaceuticals) as a 5-HT₂A receptor antagonist also stimulated research in 5-HT in hypertension, as ketanserin caused a significant reduction in blood pressure of hypertensive animals (9). However, it was discovered that ketanserin had significant affinity for the α₁ adrenergic receptor, and this interaction was thought to be primarily responsible for the fall in blood pressure. This put the field in a state of confusion as to whether 5-HT was causally involved in high blood pressure.

5-HT: good or bad guy? More recently, studies in the human suggest an elevated level of circulating plasma 5-HT in hypertensive vs. normotensive subjects (1); elevations in free plasma 5-HT have also been observed in laboratory models of hypertension (10). Our laboratory has pursued the hypothesis that there is a receptor switch in hypertension. 5-HT has significantly higher affinity for the 5-HT₂B receptor compared with the 5-HT₂A (300-fold higher in the rat). We hypothesized that the significant increase in potency of 5-HT was due to increased expression and function of the 5-HT₂B receptor. Western analyses, pharmacology, and whole animal experiments using a 5-HT₂B receptor antagonist (LY-272015) in two different models of hypertension (mineralocorticoid based and nitric oxide synthase inhibited) suggest that endogenous activation of the 5-HT₂B receptor supports elevated blood pressure (8, 11). The physiological relevance of 5-HT to a blood vessel was underscored with the discovery that systemic arteries and veins synthesized, take up, metabolize, and contain 5-HT (4, 6). These studies place 5-HT as being a pathological factor in hypertension.

However, evidence exists that contradicts this view. First, infusion of 5-HT intravenously chronically (1 wk) did not increase blood pressure of the normal or hypertensive rat, but decreased blood pressure (2). This parallels the observations made by acute injection of 5-HT which McGregor and Smirk (5) showed in this paper. 5-HT causes a rapid reduction in blood pressure, followed by a pressor response (that is exacerbated in hypertension), and then a prolonged depressor response. Second, 5-HT receptor antagonists other than ketanserin have proved equivocal in their ability to reduce hypertension (10). Thus, the question still remains: does 5-HT play a role in control of normal vascular tone, and in particular the elevated vascular tone observed in hypertension?

I had the opportunity to communicate with Don McGregor while writing this essay, and this was a privilege for me. I discovered that he developed the perfused mesenteric artery preparation as part of his PhD research, for which Dr. Smirk was his supervisor. Dr. McGregor, following this work in hypertension, returned to studies in zoology, was in university administration, and then the New Zealand government chief scientific officer. He now spends most of his time with the Environmental Risk Management Authority of New Zealand, a parallel institution to the US Environmental Protection Agency. He relates wonderful stories about Dr. Smirk during the time of this discovery. “Sir Horace was a tall man, who took rapid, giant strides down the corridors of the medical school and the hospital, with his white coat blowing out in the slip-stream behind him and doors swinging vigorously. He was first and foremost a clinician, but had a great love and devotion to experimental research, which he transmitted to others, like me”. I feel incredibly fortunate to have been able to talk with Dr. McGregor and let him know that his work with Dr. Smirk left a rich legacy for serotonergic researchers.

REFERENCES


